REMARKS

The last Office Action of January 15, 2003 has been carefully considered. Reconsideration of the instant application in view of the foregoing amendments and the following remarks is respectfully requested.

Claims 1, 4-8, 33-36, 39 and 42-50 are pending in the application. Claims 1, 4, 33, 39, 42, have been amended. Claims 2-3 and 9-32 and 40-41have been canceled. No new Claims have been added. A total of 20 claims are now on file. No claim surcharge is believed due.

It is further noted that claims 33, 39 and 41 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 39-40 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4-6, 33, 39, 41-45 and 49 stand rejected under 35 U.S.C. §102(b) as being anticipated by WO90/02176 (hereinafter "Horwich").

Claims 7, 8, 33-36, 42-43, 46-48 and 50. stand rejected under 35 U.S.C. §103(a) as being unpatentable over Horwich in view of U.S. Pat. No. 5,928,636 (hereinafter "Alber").

REJECTION OF CLAIMS 33, 39 AND 41 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Applicant has amended claims 33 and 39 and cancelled claim 41 to address the problems raised by the Examiner.

The Examiner has pointed out that the claim recites "a heterologous gene of up to 800 nucleotides in length...." which would not provide enablement for replication defective recombinant Human HBV virus and recombinant DHBV virus containing a heterologous gene of any size. Claim 33 and 39 as now amended clarifies that the size of the heterologous gene refers to a gene of the length of the 800 bps. Support for this is found in the description on page 12 line 12. It is believed that thereby the Examiners' commentary with respect to the issues on pages 3-6 of the Official Action have been addressed and obviated. Specifically, with respect to the Examiners postulation on page 4 paragraph (a) rejection on the ground of lack of enablement has been eliminated by clarifying the length of the sequences of up to 800 bp.

With respect to the Examiners commentary under paragraph (b) and (c) and in response to the Examiner's citation of the reference to Protzer et al. (Proc. Natl. Acad. Sci. 96:10818-10823;1999; IDS), applicants submits that their method provides a novel method which has received favorable comment by Don Ganem published in PNAS 96 (1999): 10818-10823, which described the instant hepadnavirus vector system dev loped as follows: "Protzer et al report a major

advance in hepadnaviral vectoring".... "the hepadnaviral genome is blanketed with critical cis-acting elements...by diligent screening they have identified a region of the viral genome that evidently lacks important cis-acting sequences and therefore tolerates substitution with foreign DNA"..."work in several laboratories for.... more than a decade..... have vigorously pursued this possibility, but successes have been few".

Withdrawal of the rejection of these claims under 35 U.S.C. §112, first paragraph is thus respectfully requested.

REJECTION OF CLAIMS 39-40 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Applicants have amended claims 39 to avoid the insufficient antecedent basis and to clarify the invention. As a result of the amendment to claim 39, the rejection under 35 U.S.C. §112, second paragraph of claim 39 and 40 is believed to have been avoided.

Withdrawal of the rejection of the claims 39-40 under 35 U.S.C. §112, second paragraph is thus respectfully requested.

REJECTION OF CLAIMS 1, 4-6, 33, 39, 41-45 and 49 UNDER 35 U.S.C. §102(b) AS BEING ANTICIPATED BY HORWICH

The rejection under 35 U.S.C. 102(b) is respectfully traversed.

The Examiner has now rejected the prior amended claims as unpatentable over Horwich. It is noted for the record that the Horwich reference is cited in the IDS submitted in the instant application and was considered when preparing and filing the application. In claim 39, the limitation "the gene encoding a heterologous gene" was eliminated. Furthermore, the phrase "a region of one of an S gene" was replaced by –sequences of the S-gene–. It is believed that claims 1, 4-6, 33, 39, 41-45 and 49 as now amended are clearly distinguishable over this reference for reason which will be set forth hereinafter.

Horwich teaches that replication defective hepadnaviruses can be produced in hepatoma cells by trans complementation of lacking gene products. In a "particle defective genome", hepadnaviral genes, e.g. pol, env, core have been knocked out. Thus, the "particle defective genome" is not able to form hepadnaviral particles on its own. Horwich discloses the use of a "packaging genome" or a packaging cell line which can express the lacking gene products and supply them in trans for packaging the "particle defective genome". This shows however that Horwich discloses only the production of hepadnaviral particles carrying a defective genome using that method. Horwich discloses that a defective hepadenaviral genome ("packaging genome") is able to produce messenger RNAs capable of supplying functions required *in trans* for packaging. Equivalent findings are described in the applicants' own publications (Se Junker Niepman, M., Bartenschlager, R G. & Schaller, H. (1989) Cell 56, 85-92).

Applicants were thus aware of those findings and noted them as part of the prior art to applicants invention.

Significantly, Horwich does not disclose nor teach that a heterologous gene sequences can replace the gene coding for the surface antigen. Rather, Horwich inserts a synthetic linker (nt. 1290 to 1358) into the S-gene such that part of the S-gene sequences were replaced. This linker, however, contains exactly the same nucleotide sequence as the replaced S-gene except for a three nucleotide exchange. (Figure 8A). The three nucleotides were exchanged to "knock out" DHBV genes in order to generate "particle defective genomes". Thus Horwich, exchanged only 3 nucleotides in the S-gene. Horwich neither inserts heterologous sequences into the S-gene nor does Horwich disclose the production of defective heapdnaviral particles containing heterologous genes as claimed here. Of course, these hepadnaviruses retain the Pre-S-DNA sequences which contain the promoters for surface antigen expression. This expression however was eliminated by the three nucleotide exchange which knocked out S-gene expression in their setting.

Thus, contrary to the Examiner's assertion, Horwich neither discloses insertion of heterologous sequences into the S region nor did it disclose the production of defective hepadnaviral particles containing heterologous genes. Horwich only discloses that part of the S gene in DHBV is replaced by a synthetic linker (nt. 1290 to 1358). This linker, however, contains exactly the same nucleotide sequence as the replaced S gene with the exception of a three

nucleotide exchange (s Figure 8A). The thr e nucleotides wer exchang d in order to knock out DHBV genes so as to generate "particle defective genomes".

Horwich describes that initiation signal, including the ATG initiation codon and adjacent signals, are required for efficient translation of protein coding sequences inserted into an expression plasmid (page 35, first paragraph). They describe this as a basis for the production of their plasmid constructs expressing "particle defective genomes" and "packaging genomes". As this requirement is general knowledge, established decades ago, the experienced artisan would be aware of this.

Furthermore, there is no showing that the system as disclosed in Horwich produces defective particles at a titer level competent to infect hepatocytes nor has infectivity of any HBV particle produced been shown or proven.

In view of the foregoing, it is clear that the claims as amended are patentably distinguished over the Horwich reference and that Horwich does not anticipate the present invention as claimed.

Withdrawal of the rejection of claims 1, 4-6, 33, 39, 41-45 and 49 under 35 U.S.C. §102(b) is thus respectfully requested.

REJECTION OF CLAIMS 7, 8, 33-36, 42-43, 46-48 AND 50 UNDER 35 U.S.C. §103(a) AS BEING UNPATENTABLE OVER HORWICH IN VIEW OF ALBER

The Examiner's rejection is respectfully traversed.

Horwich shows that a duck hepatitis B virus particle containing a "particle defective genome" which means a genome, in which the S gene was knocked out, is produced by trans- complementation of the lacking envelope gene products. Horwich furthermore shows that the S-deficient hepadnavirus produced is infectious if incubated on primary duck hepatocytes (Figure 9). However, nothing is said about a titer nor is the titer of the defective particles determined anywhere. Furthermore, Horwich does not generate a particles into which foreign sequences have been inserted and therefore does not show that any "recombinant hepadnavirus particles capable of expressing a heterologous gene in hepatocytes... at a titer level competent to infect hepatocytes" were produced.

The Examiner has now combined the Horwich reference with a newly cited reference, Alber. Based on the following, it is clear that the Examiner's combination of the two references cannot teach the claimed invention.

While the Alber reference states that a combination of IL-12 and IFNα together with a pharmaceutically acceptable carrier is "effective in treatment and prophylaxis of infectious diseases,..... e.g. Hepatitis B.....these compositions are characterized by the synergistic interaction of IL-12 and IFNα. This does not mean that by combining the references one could arrive at the claimed invention. In particular, Alber claims that recombinant proteins IL-12 and INFα if applied

together are suitable for a treatment of various infectious diseas s caused by viruses, bacteria or parasites.

In contrast, what is claimed in the present invention is that local expression in the liver(cells) of IFNα or another pro-inflammatory cytokine can be obtained with the help of recombinant protein. Applicants neither intend to express any recombinant protein, nor is a recombinant protein systematically applied (as proposed by Alber); nor is it intended to or is IL-12 and IFNα co-express with the help of recombinant hepadnavirus genomes. Clearly, the latter is precluded due to the size restriction of the hepadnavirus. Consequently, the teachings of Alber do not point into the direction of the claimed invention even when combined with the teachings of Horwich. Moreover, the vector system in Alber is an adeno associated vector which has broad application and not suitable to a comparison with the claimed vector system.

The Examiner states that it would have been obvious and within the scope of skill for an ordinary skilled artisan to modify the replications defective recombinant hepadnavirus and methods for expressing a heterologous gene in a hepatocyte and for producing replication defective recombinant hepadnavirus particles taught by Horwich by using a gene encoding IFNα or other interferons (e.g. IFNγ) or IL-12 as the heterologous gene in light of the teachings of Alber.

This postulation is fatally flawed since Horwich precisely does not show that a heterologous gene was inserted. Thus from that point of view the stated expression in Horwich would not work with the facts as pr sented here.

Conv rsely, Alber using a required co- xpression system altogether teaches away from the claimed replication defective particle.

It is also pointed out in this context that Alber claims broadly a pharmaceutical composition for parenteral administration to a human patient and a method for treatment of a human patient complete with doses per human weight when the 2 examples show only experimentation on mice.

For the reasons set forth above, it is applicant's contention that neither Horwich nor Alber, nor a combination thereof teaches or suggests the features of the present invention, as recited in claims 7, 8, 33-36, 42-43, 46-48 and 50.

As for the rejection of the retained dependent claims, these claims depend respectively on claims 1, 33, 39, 42 share its presumably allowable features, and therefore it is respectfully submitted that these claims should also be allowed.

Withdrawal of the rejection of claims 7, 8, 33-36, 42-43, 46-48 and 50 under 35 U.S.C. §103(a) and allowance thereof are thus respectfully requested.

The amendments to claims 1, 4 and 42 are "cosmetic" to conform to non-statutory formal requirements imposed by the U.S. Patent and Trademark Office. notwithstanding applicant's belief that claims 1, 4 and 42, as originally filed in this context were clear. Accordingly, applicant asserts that the amendments to claims 1, 4 and 42 have not narrowed these claims within the meaning of the *Festo*-decision. *Festo Corp. v. Shoketsu Kinsoku Kogyo Kabushiki Co.*, 56 USPQ2d 1865 (Fed. Cir. Nov. 29, 2000)(en banc).

CONCLUSION

Applicant believes that when the Examiner reconsiders the claims in the light of the above comments, he will agree that the invention is in no way properly met or anticipated or even suggested by any of the references however they are considered.

None of the references discloses a method for expressing a heterologous gene in hepatocytes, wherein the sequences of the S-gene haven been replaced with heterologous gene of the size as claimed and which accomplishes delivery in the hepatocytes.

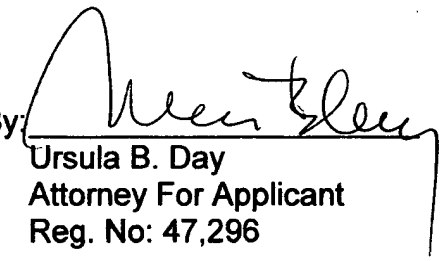
In view of the above presented remarks and amendments, it is respectfully submitted that all claims on file should be considered patentably differentiated over the cited art and should be allowed.

Reconsideration and allowance of the present application are respectfully requested.

Should the Examiner consider necessary or desirable any formal changes anywhere in the specification, claims and/or drawing, then it is respectfully requested that such changes be made by Examiner's Amendment, if the Examiner feels this would facilitate passage of the case to issuance. If the Examiner feels that it might be helpful in advancing this case by calling the undersigned, applicant would greatly appreciate such a telephone interview.

The Commission r is hereby authorized to charge fees which may be required, or credit any overpayment to Deposit Account No. 50-1747.

Respectfully submitted,

By: 

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